Peer reviewed article

Echocardiographic quantification of atherosclerosis leads to cost-effective treatment with statins

Data from a prospective study of 336 patients

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Summary

Objective: Use of statins in prevention of atherosclerosis is effective but expensive. Patient selection gains wider public attention as medication costs in the US and Europe augment by 8% to 10% per year. We examined different clinical risk stratification strategies, particularly focusing on echocardiographic atherosclerosis quantification, for their impact on event reduction and cost-effectiveness in statin treatment.

Methods and Results: In a prospective, consecutive cohort of 336 patients referred to non-invasive cardiac examination, risk stratification was done by various combinations of risk factors and non-invasive atherosclerosis quantification. Atherosclerotic burden was determined through measuring "aortic elastance" by transthoracic echocardiogram, a validated non-invasive method. Cardiovascular events were recorded at a mean follow-up of one year. Echocardiographically determined atherosclerosis severity and event history, especially in combination, yielded the best selection strategies for statin treatment over a broad range of predetermined funding or required event reductions, surpassing conventional cardiovascular risk factors. From 26.8 statin-preventable events/1000 patients/year (assuming all patients treated), the best selection strategies could avoid: 24 with 66% of the cost for statin treatment (atherosclerosis and age criteria), 20.1 with <50% of the budget, 12.2 with <30% of the budget or 9.6 with <15% of the budget (using combinations of atherosclerosis and prior events), while conventional strategies without echo quantification of atherosclerosis were inferior.

Conclusion: Non-invasive echocardiographic quantification of atherosclerosis improves efficiency and cost-effectiveness in statin treatment.

Key words: echocardiography; atherosclerosis; cost-effectiveness; statin; stratification

Introduction

Atherosclerosis and its complications such as myocardial infarction, stroke and peripheral vascular disease are leading causes for morbidity and mortality in western countries. Primary and secondary prevention have shown to be effective, including life-style changes and/or pharmacological prevention [1–6]. Trials like AFCAPS/TexCAPS [1] and ASCOT-LLA [2] showed that statin treatment is effective in large populations. Although prevention by life-style changes is inexpensive and desirable, it is, as an isolated measure, often not sufficient to reduce cardiovascular risk to a desired level. Therefore, treatment with statins is an important issue, even though such treatment is expensive and drugs may have to be taken over many years.

In times of restricted resources, it is important to distribute them as effectively as possible. Cost-effectiveness of lipid-lowering therapies is thus an ongoing debate [7]. To answer the questions which patients will profit most from statin treatment, to what extent lipid lowering should be administered in the general population and how cost-effectiveness can be improved, additional stratification methods are needed.

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Conventionally, statin therapy is initiated in patients with prior events, hyperlipidemia or other risk factors, or a high risk score computed in various ways (eg, Framingham risk score, which takes in account gender, age, total cholesterol, HDL-cholesterol, smoking and systolic blood pressure; or, for european males below the age of 65, the PROCAM algorithm).

Thus, high-risk constellations used for stratification typically ignore the actual extent of the atherosclerotic process itself, the *sine qua non* for atherosclerotic complications. This process plays only a small role in the actual risk stratification, because measurement of atherosclerosis severity has technically been difficult. However, there have been recent advances in non-invasive determination of atherosclerosis severity, which now can be done as a bedside investigation with standard echocardiographic equipment and with proven prognostic implications [8].

We hypothesised that direct echocardiographic quantification of atherosclerosis will improve patient selection and thus cost-effectiveness of statin treatment because it is directly linked to the fundamental pathophysiological process, compared to the classical "risk factors" which are only indirectly linked to cardiovascular events through the intermediary of atherosclerosis (figure 1). Thus, we analysed data from a prospective cohort study that analysed techniques of non-invasive atherosclerosis quantification [8], focussing here on the selection of cost-effective risk stratification strategies.

Methods

The study was designed to test the usefulness of different methods of cardiovascular risk stratification. Special emphasis was put on statin treatment in order to find different levels of cardiovascular risk and financial expenditure as well as the absolute and relative number of events that can potentially be avoided with statin treatment.

Study design

In a consecutively collected study cohort of patients referred for non-invasive cardiovascular assessment to three centres, the severity of atherosclerosis was measured non-invasively, conventional risk factor assessment was done, and the occurrence of major cardiovascular events was monitored for one year. The predictive value for major adverse cardiovascular events of conventional risk factors and of non-invasive atherosclerosis quantification in this cohort was analysed as reported in a separate paper [8]. Based on observed cardiovascular event rates in subgroups as well as on actual statin intake, a statistical model was then designed that allowed studying the impact on major cardiovascular events of statin treatment in different subgroups (see below). A number of different stratification strategies were then applied to this cohort model to assess the impact on event reduction.

Observed and modelled event risk

Based on actual observed cardiovascular events and actual statin intake, as well as on relative risk reduction data from the statin megatrials, the number of avoidable events was calculated for the subgroup not on statins, and the number of avoided events was calculated for the subgroup that was on statin treatment. This is reasonable because *relative* risk reduction in most subgroups of the statin megatrials was similar, even when *absolute* risk reducation varied significantly due to marked differences in absolute risk in different groups in those studies. This constant relative risk reduction allows calculation in treated patients of the expected number of additional events without treatment and vice versa as shown in the text box.

Relative risk reduction under statin treatment was expected to be 33.3%, because primary prevention trials had shown relative risk reductions between 30% and 37% [1–3, 9] corresponding to relative risk in treated patients of 66.6% (63 to 70); and secondary prevention trials had shown relative risk reductions in a comparable range [6].

Atherosclerosis severity

Atherosclerosis severity was measured non-invasively using a recently described transthoracic echocardiographic approach [8] which uses specific aortic elastance as surrogate parameter for overall atherosclerosis severity. This parameter can be measured easily with limited time consumption using standard echocardiographic equipment. The method has been validated by direct visualisation of plaque burden, is robust when assessed against a broad range of possible confounding factors, has proven to be a powerful cardiovascular risk predictor, and is competitive compared to other methods that exploit arterial mechanics [10–16]. Briefly, measurement of atherosclerosis severity is based on the biomechanics of pulse wave propagation in the central arterial tree described by the Moens-Korteweg equation.

$$c^2 = \frac{E * h}{\rho_f * D} \quad \text{with}$$

c = wave propagation velocity
h = wall thickness
ρ_f = fluid density
D = vessel diameter
E = *Young's* Module

The product E*h, termed "specific aortic elastance" is increased when either wall thickness is increased (eg, due to plaque formation) or when the wall becomes stiffer due to fibrosis or calcium deposition. Specific elastance has been shown to correlate strongly with plaque burden. As described in detail in the validation paper, vessel diameter was measured as an average of three measurements at three aortic locations; aortic length was calculated as 0.41 m/m body height; blood density can be considered constant (1060 kg/m^3) and pulse wave velocity was determined from wavefront delay from the left ventricular outflow tract to the femoral artery in the groin. In practice this means that aortic diameters are measured in the ascending aorta, the aortic arch and in the subxiphoidal window are measured by 2D echo and are averaged, yielding *D*. Then pulse wave delay relative to the ECG R-wave is measured in the left ventricular outflow tract and in the groin, and the difference of these delays taken as wave propagation time; this is divided by aortic length to yield wave velocity *c*. Finally, these measurements are substituted in the formula for *Specific Elastance E*h* derived from above:

$$E^*h = \rho_f{}^*D^{*2} = 1060^* \; diameter^* \left(\frac{propagation\text{-}time}{0{,}41^* \; height} \right)^2$$

A simple web-based atherosclerosis calculator for the formula given above as well as reference values can be found at http://www.koronarsyndrom.ch.

Risk factors and scores

According to current clinical practice, demographic data were assessed and a history of known cardiovascular risk factors was taken, taking into account the variables total cholesterol, HDL-cholesterol, diabetes, smoking and hypertension, while minor risk factors like homocysteine levels and lipoprotein fractions (other than cholesterol and HDL-cholesterol) were neglected according to current clinical practice. A detailed history of cardiovascular events and procedures was taken, relying on patient and physician interviews in combination with hospital chart reviews. An untreated total cholesterol of >6.5 mMol/l, an untreated total cholesterol >5.2 mMol/l with a total cholesterol to HDL Ratio of >5 defined hypercholesterolaemia according to the guidelines in effect at the initiation of the study. As risk scores, the number of major risk factors and the Framingham score [17] were chosen because of their widespread clinical application. The Framingham score takes into account gender, age, total cholesterol, HDL-cholesterol, smoking and systolic blood pressure; it correlates with the ten year risk of coronary artery disease (CAD). As a European alternative, the PROCAM score could have been used, but was not chosen because only 120 of our 336 patients matched the PROCAM inclusion criteria (males ≤65 years).

Patients

Included were 336 consecutive patients referred for non-invasive cardiological examination. Exclusion criteria were manifest arterial obstructive disease of the aorto-iliacal axis (due to the evident limitation of measuring "wave propagation" across a vessel occlusion) and missing consent. Patients underwent echocardiographic quantification of atherosclerosis as described above. Follow-up at one year was done by telephone interview of patients and treating physicians and hospital chart review in case of events. The primary endpoint was a composite endpoint of atherosclerotic death, myocardial infarction, or stroke. To yield an additional *age corrected* measure of atherosclerosis severity, analyses were also performed after dividing the cohort into three age strata.

Treatment scenarios

A range of treatment scenarios was chosen with the aim to cover current practice, as well as to cover very liberal (all patients treated) as well as very stringent treatment

Figure 1

Direct vs indirect stratification for statin treatment. Conventional risk stratification gives little weight to actual determination of atherosclerosis severity. As atherosclerosis severity can be measured non-invasively by echocardiography, this study examines whether this measurement can be profitably used for cost-efficient patient selection for statin treatment.

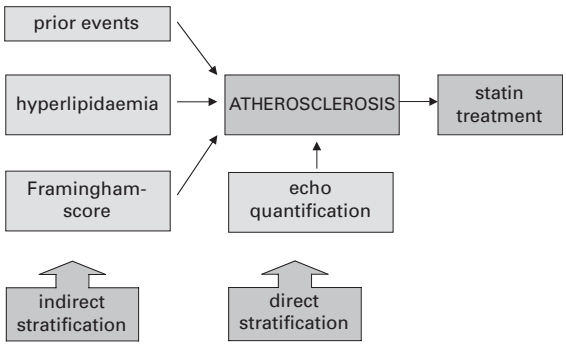


Table 1

List of different stratification scenarios and number of patients included in each scenario (pts = patients fulfilling the criterion).

atherosclerosis severity (highest tertile) (110 pts)
atherosclerosis severity (highest and middle tertile) (221 pts)
age-corrected atherosclerosis severity (highest and middle tertile) (220 pts)
prior event or for atherosclerosis severity (highest tertile) (158 pts)
prior event and atherosclerosis severity (highest tertile) (39 pts)
hyperlipidaemia and atherosclerosis severity (highest and middle tertile) (134 pts)
prior event and atherosclerosis severity (highest and middle tertile) (63 pts)
prior event (88 pts)
hyperlipidaemia (203 pts)
Framingham risk score >12.9 (107 pts)
>1 risk factor (133 pts)
>2 risk factors (59 pts)
highest tertile for age (110 pts)
prior event AND hyperlipidaemia (63 pts)
all treated (336 pts)

Table 2

Patient characteristics.

Number of patients:	336
Gender	206 Men (61%), 130 Women (39%)
Age (mean):	63 years (SD 15, range 11–92)
1st tertile	<59.6 yrs
2nd tertile	59.6 –70.5 yrs
3rd tertile	>70.5 yrs
Risk factors:	
Hypercholesterolaemia:	203 (60%)
Smoking:	87 (26%)
Positive family history:	61 (18%)
Diabetes:	49 (15%)
Hypertension:	143 (43%)
LV Hypertrophy:	*49 15%*
Number of risk factors	1.4 (SD 1.1)
0 risk factors	26%
1 risk factor	34%
2 risk factors	22%
3 risk factors	14%
≤4 risk factors	4%
LVEF (mean):	54% (SD 14)
Below 50%:	22%
Prior myocardial infarction:	62 (18%)
Prior Stroke:	32 (10%)
Prior arterial revascularisation:	44 (13%)
Blood lipids:	
Mean cholesterol	5.3 (SD 1.2) mmol/l
Mean HDL	1.3 (SD 0.41) mmol/l
Mean LDL	3.3 (SD 1.0) mmol/l
Patients on Statin Therapy:	39 (12%)

criteria. The different stratification scenarios are seen in (table 1). The first seven scenarios include echo quantification stratification. Scenario A selects a high risk population, compared to scenario B and C where patients at moderate risk are also selected. Combinations of atherosclerosis severity with a history of prior cardiovascular events are evaluated in scenario D and E. Taking two parameters into account seems realistic and practicable for daily practice. The same is true for the scenario F, where hyperlipidaemia instead of prior events is used in combination with atherosclerosis severity. Scenario G evaluates a larger proportion of patients, also including patients with moderate atherosclerosis. More conventional stratification methods are evaluated in scenarios H to O, and for reference, statin treatment of the whole cohort is described in scenario P.

The number needed to treat (NNT) per avoided event can then be calculated from the difference between the number of events if both subgroups were treated with statins and the number of events if no subgroup was treated with statins, divided by the number of events. Drug costs per avoided event were computed by multiplying NNT with the costs for statin treatment for one year. Drug costs were taken from average end user prices for statins in typical doses in Switzerland, which amounted to 560 Euros per patient and year of statin treatment (compared to 217 Euros for a transthoracic echocardiogram)

Statistics

Statistics were done using StatView Software 5.01 (Abacus Inc., Berkeley, California). Data were evaluated for normal distribution. If a normal distribution was found, standard deviation (SD) and mean were used, otherwise median and interquartile width are given. Because the surrogate parameter for atherosclerosis severity, specific elastance did not show normal distribution, data were log transformed for analysis. Event risk was calculated for tertiles of different predictors of cardiovascular events.

Results

A total of 336 patients were included; patient characteristics are given in (table 2). Median specific aortic elastance was 1.8 kN/m (interquartile width: 1.5; range: 0.2 to 23 kN/m) in the entire cohort and 2.1 kN/m in statin-treated patients. Stratification into three tertiles yielded cutoff values of 1.43 kN/m and 2.33 kN/m, respectively, for the lowest, middle, and highest tertile of atherosclerosis severity.

Follow-up was done in 99.7% of patients with one patient lost because of emigration to another continent. Including multiple events in individual patients, a total of 21 deaths occurred (9 were non-atherosclerotic deaths), 5 nonfatal myocardial infarctions and 7 strokes were observed and 21 revascularisation procedures were performed (8 coronary revascularisations, 10 bypass operations, 3 carotid interventions); events occurred in 10.3% of patients on statins and in 12.1% of untreated patients.

Counting only one endpoint per patient, the predefined primary composite endpoint of atherosclerotic death, nonfatal infarction or cerebrovascular stroke was reached in a total of 22 patients.

As reported in detail in [8], specific elastance was a strong predictor of the primary endpoint ($p = 0.0002$) with a 16-fold increase in relative risk from the lowest to the highest atherosclerosis tertile [8] (figure 5), supporting the results of the validation study [8] where specific elastance was the best correlation of the non-invasively measured parameters with directly imaged plaque burden ($R^2 = 0.76$; $p < 0.0001$).

The different calculated stratification scenarios are shown in figures 2 and 3. Figure 2 shows the relationship between the percentage of patients treated with the particular stratification scenario, compared to absolute event reduction per 1000 patients treated for one year. Diamonds mark strategies that make use of echo-quantification of atherosclerosis. Generally, adding non-invasive atherosclerosis quantification shifted the strategy towards the upper left in the graphs indicating higher effectiveness at lower cost.

The best number needed to treat to avoid one event was reached in group E combining prior cardiovascular events with severe atherosclerosis, corresponding to the lowest costs per event avoided are least in this group, although the absolute event reduction was limited in this group because more

Figure 2

Relationship between the fraction of patients treated with a particular stratification scenario, compared to absolute event reduction. Diamonds mark strategies that make use of echo-quantification of atherosclerosis. For a given drug budget for the cohort (ie, a given prescription frequency) that can be chosen on the X-axis, the number of avoidable events using different stratification scenarios can be found on the Y-axis. The diagonal line corresponds to random sampling of the cohort.

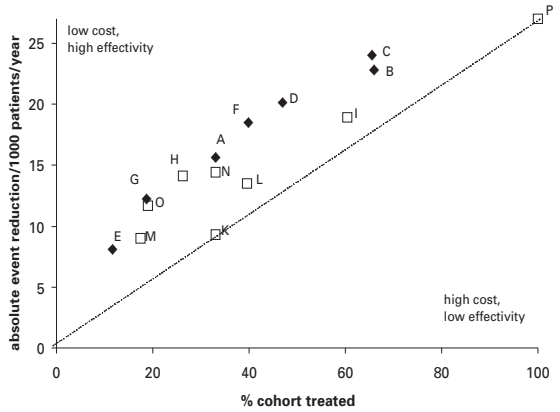
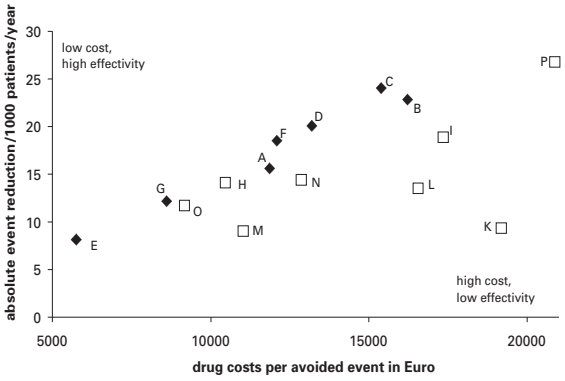


Figure 3

How many events can be avoided at what cost? Impact of different patient selection strategies for statin treatment. Diamonds mark strategies that make use of echo-quantification of atherosclerosis. An optimal strategy yields a maximum absolute event reduction at a minimal cost, ie, it is found in the upper left of the diagram, while ineffective selection strategies have a small impact on overall event rate, but have a large cost per avoided event (lower right). Note that strategies that include atherosclerosis measurement tend to the upper left, an observation valid for multiple spending levels.



cumulative events occurred in the much larger proportion of patients at moderate risk. Compared to treatment of all patients, withholding of statins of those in the low atherosclerosis tertile still prevented most events.

Table 3 summarises the results of the different treatment strategies in a side by side view.

Figure 3 observes the data from a different point of view: how much do I want to spend to avoid one event, and how many events can be avoided overall with a given strategy? Again, it was seen that combination of atherosclerosis quantification methods shifted the curve to the upper left, again indicating "low cost – high effectiveness".

Discussion

The question of patient selection for prevention of atherosclerosis is of prime importance, first because a large proportion of our population will develop atherosclerotic disease and will eventually die from it, and second, because widespread, unfocused statin medication carries the risk of breaking our public healthcare systems due to the significant price tag of these drugs. Optimal prevention strategies will therefore not only give those at high risk an optimal benefit, but will also allow spending the healthcare budget wisely, so that the healthcare system can afford to treat them at all.

The present study highlights that the presence and extent of atherosclerosis is not only of patho-

Table 3

Absolute event reduction, number needed to treat and drug cost per avoided event for each stratification scenario. Calculation with 33.3% expected risk reduction by statins, (brackets: range for expected risk reduction by statins of 30% and 37%, respectively). NNT = Number needed to treat.

	Patients treated	Absolute event reduction / 1000 patients / year	NNT/ event avoided	Drug costs per avoided event (Euro)
A	Atherosclerosis severity [highest tertile]	15.6 (13.8–17.6)	21.2 (18.7–23.9)	11 864
B	Atherosclerosis severity [highest & middle tertile]	22.8 (20–25.6)	29 (25.9–33)	16 229
C	Age-corrected atherosclerosis severity [highest & middle tertile]	24 (19.4–27.7)	27.5 (23.8–34)	15 389
D	Prior event OR atherosclerosis severity [highest tertile]	20.1 (18–23.2)	23.6 (20.5–26.7)	13 207
E	prior event AND atherosclerosis severity [highest tertile]	8.1 (7.1–9)	14.5 (13–16.5)	5760
F	hyperlipidaemia AND atherosclerosis severity [highest and middle tertile]	18.5 (16–21.6)	21.6 (18.6–25)	12 088
G	prior event AND atherosclerosis severity [highest or middle tertile]	12.2 (11.2–14.8)	15.4 (12.8–16.9)	8618
H	prior cardiovascular event	14.1 (11.6–15.8)	18.7 (16.7–22.8)	10 465
I	hyperlipidaemia	18.9 (16.6–21.3)	31 (27.1–35)	17 348
K	Framingham risk score >12.9	9.3 (8.5–10.6)	34.3 (30.4–37)	19 195
L	>1 risk factor	13.5 (11.9–15.4)	29.6 (25.9–33.7)	16 564
M	>2 risk factors	9 (7.7–10.1)	19.7 (17.5–22.9)	11 024
N	highest tertile for age	14.4 (12.6–16)	23 (20.6–26.1)	12 871
O	prior cardiovascular event AND hyperlipidaemia	11.7 (10–13.1)	16.4 (14.4–19)	9178
P	all treated	26.8 (16.6–32.6)	37.3 (31–41)	20 873

physiological importance for development of atherosclerotic complications, but atherosclerosis severity can also be evaluated non-invasively at the bedside; such measurement can profitably be used for selection of an optimal cardiovascular prevention strategy, independent from the desired risk threshold chosen or from the budget one is willing to spend per avoided event.

Evidently, those patients who have already suffered a manifestation of atherosclerosis are at high risk by this simple fact (although even in this population, underlying atherosclerosis severity still matters), but the overall impact on event number remains limited because many events occur in a population at moderate risk. More important is the question, which additional "risk factors" should be taken into account for prevention in those who have not yet suffered an event. In view of the ever-growing number of *statistically* significant risk factors (often detectable only in very large databases), simple algorithms for individualised treatment decisions, which are nevertheless as powerful as possible, are needed to render this approach practicable. This study argues that atherosclerosis severity itself is not only a key variable in the pathogenetic process and therefore in predicting individual risk, but is also helpful for choosing an appropriate treatment decision in an individual person.

While the recognition of hypercholesteraemia as a risk factor [18] and observation of risk reduction through lowering of a pathologically high cholesterol level [6] made this measurement of prime importance for initiation of statins in earlier years, today, the awareness that statin effects are quite independent from plasma cholesterol [2, 4, 19] together with the recognised pleiotropic statin effects [20] have led to less reliance on plasma cholesterol alone for initiating statin treatment. In addition to patient history and conventional risk factors, a range of tests is available that attempt to stratify risk by assessing atherosclerosis severity. They include ultrasound methods like measurement of carotid intima-media thickness, strongly advocated by some [21], while others doubt its value in the individual [22]. Other methods are based on calcium detection by computed tomography [23–25] – a method associated with radiation exposure which is not undisputed, while magnetic resonance imaging is also able to visualise atherosclerosis [26, 27] without radiation, but at a cost that renders applicability in a general population questionable. Studies that compare the usefulness of such methods head-to-head will certainly be important in the future.

The echocardiographic method used for atherosclerosis quantification in the present study is not the only one that is based on central arterial mechanics [10–16]. We prefer it to others because it has not only a strong basis in biophysics but has also been validated by direct visualisation of plaque burden, has proven powerful in risk prediction [8], can be performed by a physician experienced in echocardiography in a minimum of time, and does not need additional equipment.

There are also limitations to this study: although based on actual outcomes in a multicentre setting, this is not a randomised trial; such a large, randomised trial would be welcome, but for a technique that does not widen the indications for a drug but rather focuses drug use, the financing would be difficult. The fact that a cohort referred for non-invasive cardiological examination was studied represents bias, and results can therefore best be applied to similar groups of individuals; more data in other patient groups are needed (currently such studies are ongoing, as are studies with a longer follow up). Another limitation is the use of same *relative* risk reduction with statin treatment for all patients, a finding that has been confirmed in most subgroups in the statin megatrials, but not in all [1, 5]. Full cost effectiveness calculations might also include costs incurred by physician visits and laboratory tests as well as costs saved through avoided events [28], as well as indirect costs, although this would not weaken the key message of this paper, namely that improved targeting of the use of an expensive drug will improve cost-effectiveness. Finally, larger cohorts/longer observation periods with more events are desirable to render calculations more robust.

Clinical implementation of echocardiographic atherosclerosis quantification in view of statin prophylaxis appears straightforward as the necessary equipment for the simple technique is widely available, an echocardiographic examination is less than half as costly as statin treatment for one year, and the examination yields additional prognostic information such as left ventricular hypertrophy, left ventricular ejection fraction as well as information about the presence of an abdominal aortic aneurysm, all of which may have therapeutic consequences.

We conclude that cost-efficiency of atherosclerosis prevention by statin treatment can be optimised by non-invasive, echocardiographic quantification of atherosclerosis.

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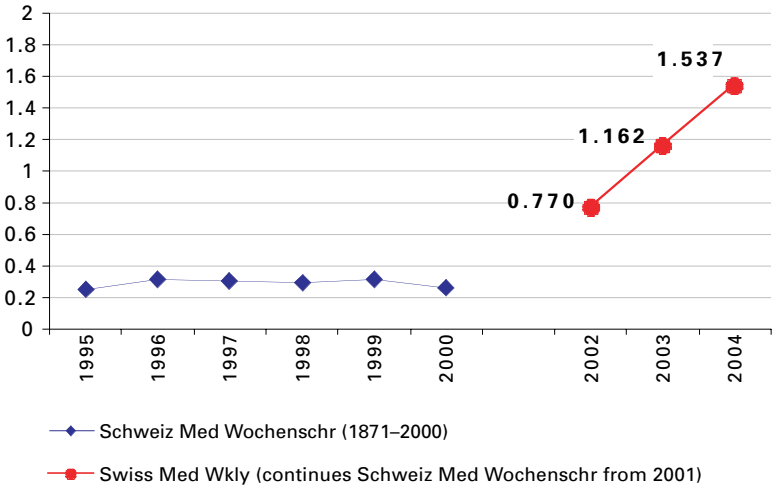

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